

REMARKS/ARGUMENTS

Claims 1 and 3-29 were pending in the above-identified application. Claims 4-7, 10-12, 16, and 24-29 have previously been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1, 3, 8-9, 13-15, and 17-23 have been acted upon by the Examiner. Claims 1, 19 and 20 have been amended as further discussed below. No new matter has been added by the amendments. In light of the above amendments and the remarks and arguments set forth below, Applicants respectfully request reconsideration of the application.

Rejections under 35 U.S.C. § 112

The prior rejection under 35 U.S.C. § 112, first paragraph has been withdrawn.

Rejections under U.S.C. § 102

Claims 1, 3, 8, 9, 14, 17 - 19, and 23 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Bernard *et al.*, 1998 (of record). Bernard *et al.* is again alleged by the Examiner to teach a method comprising culturing non-activated monocytes (*i.e.*, a monocytic dendritic cell precursor) with GM-CSF alone in a TEFLON™ culture bag (*i.e.*, a bag comprising PFTE). Bernard *et al.* is alleged to further teach that the culture system is adherent free, and that the resulting cells express CD1a (see Fig. 2, in particular). Bernard *et al.* is also alleged to teach that the monocytes are isolated by apheresis and contacting the CD1a⁺ cells with the bacterial antigen tetanus toxoid.

The Examiner also believes that the instant claims are drawn to a method of differentiating dendritic cells employing a dendritic cell precursor (*i.e.*, a method of using a product made by a particular process). The Examiner asserts that from this conclusion therefore the method by which the monocytic precursor is produced does not carry patentable weight in the absence of a structural difference. The monocytic dendritic cell precursors of Bernard *et al.* are asserted by the Examiner to be the same as those produced by tangential flow filtration. Additionally, the Examiner has asserted that while Bernard *et al.* do not characterize the CD1a⁺

cells as immature dendritic cells, they must inherently be immature dendritic cells, since they are produced by a method identical to that of the instant claims. Based on these allegations, the Examiner asserts that the reference clearly anticipates the invention.

The Examiner has considered Applicants' prior argument but has found it unpersuasive. In particular, the Examiner has reiterated the allegation that Bernard teach the exact method of the instant claims in that non-activated monocytes are cultured with GM-CSF alone in a bag comprising PFTE. Furthermore, the Examiner points to Figure 2 in Bernard as showing the resulting cells expressing CD1a at approximately one half log higher intensity than the starting population of monocytes and therefore has concluded that the method of Bernard results in a cell displaying the exact same structural properties as recited in the instant claims. The Examiner has in particular noted the characteristic of expressing CD1a on the cell surface.

It has been noted by the Examiner that Bernard characterizes the GM-CSF only cells as macrophages and that the cells do not demonstrate significant neo-expression of CD1a by the macrophage, but the Examiner does not believe that the instant claims are limited to cells expressing CD1a to a "significant" degree. Further, the Examiner believes that since Bernard has performed the exact method of the instant claims, they must inherently have obtained immature dendritic cells. In addition, the Examiner has asserted that the fact that Bernard fail to recognize the inherent properties of the resulting cells is not relevant. Still further, the Examiner notes that a reference is no less anticipatory if, after disclosing the invention, the reference then disparages it, asserting "the fact that Bernard et al. fail to recognize the cells as immature dendritic cells, or characterize the level of CD1a expression in Fig. 2 as "not significant" is not relevant. The Examiner believes that the reference nevertheless discloses the method resulting in the production of CD1a expressing cells of the instant claims.

Applicants respectfully disagree with the rejection of claims 1, 3, 8, 9, 14, 17 - 19, and 23 as being anticipated by Bernard *et al.* In particular, Bernard *et al.* do not disclose the exact method of the present invention. As previously submitted Bernard *et al.* only disclose a method of differentiating monocytes into macrophage cells by culturing in GM-CSF alone

without any additional cytokines. The method for the production of macrophage comprises culturing monocytes with GM-CSF alone. The macrophage were characterized by the absence of significant neo-expression of CD1a and CD1c, a much lower expression of HLA DQ molecules and an up-regulation of CD14. See page 21, right column 26 - 32. It is well known in the art that CD14 is a defining cell surface marker of macrophage and is not present or is greatly reduced on the cell surface of immature dendritic cells. Applicants note that the instant claims are directed to immature dendritic cells that express CD1a on their surface and not macrophage. As such, Bernard *et al.* do not anticipate the method of the present invention.

The Examiner has also asserted that the monocytic dendritic cell precursors of Bernard *et al.* (e.g., monocytes isolated by elutriation) are inherently identical to the monocytic dendritic cell precursors produced by tangential flow filtration. As there is no characterization of the precursor cells following elutriation, the Examiner has no basis to make this assertion. The fact that IL-4 was apparently necessary to prevent differentiation of the precursor cells of Bernard *et al.* when cultured in "non-adherent" conditions would suggest that the precursor cells may have been activated during elutriation or that there is a factor in the culture media of Bernard *et al.* that is activating the monocytes to differentiate into macrophage without IL-4. As such, Applicants do not believe that the Examiner has demonstrated that the dendritic precursor cells of Bernard are inherently identical to the precursor cells of the present invention.

In order to further expedite prosecution of the present application and to further clarify the claimed method, Applicants have amended claims 1, 19, and 20 to recited "for the human monocytic dendritic cell precursors to differentiate into immature dendritic cells having decreased expression of CD14 and having increased expression of CD1a on the cell surface". This amendment is believed to further clarify that the immature dendritic cells are not the same as macrophage by explicitly noting the reduction of absence of CD14 on the surface of the immature dendritic cells. As such, the final product of the claimed invention is clearly not the same as that of Bernard and it is not that Bernard did not recognize that the cells produced by using GM-CSF alone were not immature dendritic cells. Bernard clearly measured the presence

of CD14 and CD1a on the surface of the cells obtained using GM-CSF alone and GM-CSF in combination with IL-4. The two methods did not result in the same cell product.

Applicants respectfully request that the rejection of claims 1, 3, 8, 9, 14, 17 - 19, and 23 as being anticipated by Bernard *et al.* be reconsidered and withdrawn in view of the above amendments and remarks.

Rejections under U.S.C. § 103

Claims 1, 3, 8, 9, 13, 14, 17 and 18 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Matera *et al.*, 2000, in view of Bernard *et al.*, 1998 (above). In particular, as set forth previously the Examiner alleges that Matera *et al.* teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting (*i.e.*, non-activated), and contacting the monocytes with GM-CSF in the absence of additional cytokines citing to page 30 and 31 in particular. Matera *et al.* is also alleged by the Examiner to teach culturing in a serum free medium and to teach that the dendritic cells generated by culture with GM-CSF alone express CD1a. The Examiner has also alleged that the monocytic dendritic cell precursors of Matera *et al.* are the same as those produced by tangential flow filtration. Matera *et al.* is acknowledged by the Examiner not to teach a low avidity culture vessel comprising PFTE.

As above, Bernard *et al.* is alleged by the Examiner to teach a method to generate dendritic cells from purified blood monocytes by culturing in a TEFLON™ (comprising PFTE) bag. Furthermore, the Examiner has alleged that Bernard *et al.* teaches that the method meets good laboratory practice (GLP) procedures necessary for the clinical use of dendritic cells. Therefore, the Examiner believes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the dendritic cells taught by Matera *et al.*, using the TEFLON™ culture vessel, as taught by Bernard *et al.*. Motivation for the ordinary artisan at the time the invention was made would have been provided since Bernard teaches that this method is useful for clinical purposes, since it involves the large scale differentiation of

dendritic cells in a culture system that meets GLP procedures. Moreover, one of ordinary skill in the art would have a reasonable expectation of success.

The Examiner has considered Applicants prior arguments and does not consider them persuasive. In particular, the Examiner believes that the instant claims are not limited to using GM-CSF alone and can include other non-cytokine elements. The Examiner notes that Matera use combinations of GM-CSF and the hormone prolactin.

Applicants respectfully disagree with the rejection of claims 1, 3, 8, 9, 13, 14, 17 and 18 as being unpatentable under 35 U.S.C. § 103(a) over Matera *et al.*, 2000, in view of Bernard *et al.* Matera *et al.* is alleged by the Examiner to teach a method of differentiating dendritic cells comprising providing a population of peripheral blood monocytes that have been selected by magnetic sorting (a non-activating method) and contacting the non-activated monocytes with GM-CSF in the absence of additional cytokines. To the contrary, Matera *et al.* disclose a method for differentiating a population of peripheral blood monocytes that have been selected by magnetic sorting and contacting with various agents. Applicants respectfully note that contact of monocytes with a CD14 specific antibody activates the monocytes. See for example, Schutt *et al.*, *Immunol. Lett.* 4:321-327, 1988, entitled "Human monocyte activation induced by an anti-CD14 monoclonal antibody". (Abstract attached). As such, Matera does not teach or suggest a method directed to non-activated monocytic dendritic cell precursor differentiation.

Bernard *et al.* is described above, and like Matera *et al.* do not describe or suggest a method as disclosed and claimed in the present application. As both Matera and Bernard teach methods involving the differentiation of activated monocytes, there is no disclosure in either reference when considered alone or in combination that suggests or teaches the present invention. The Examiner is respectfully requested to therefore reconsider and withdraw the present rejection.

Claims 19-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Matera *et al.* and Bernard *et al.*, as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, in further in view of Bosch *et al.*, 2001 (of record). The teachings of Matera *et al.* and Bernard *et al.* are described above. The Examiner has acknowledged that they not teach generating maturing the dendritic cells with IFN γ and BCG. Bosch *et al.* is alleged by the Examiner to teach that dendritic cells can be matured with a combination of IFN γ and BCG (*i.e.*, a bacterial antigen). Additionally, Bosch *et al.* is alleged by the Examiner to teach that maturation with IFN γ and BCG results in a dendritic cell population that can induce an immune response against a tumor antigen in cancer patients.

Therefore, the Examiner has asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a dendritic cell, as taught by Matera *et al.* and Bernard *et al.*, followed by maturation with BCG and IFN γ as taught by Bosch *et al.*. The Examiner has asserted that the ordinary artisan would have been motivated to do so, since Bosch *et al.* teach that IFN γ and BCG are extremely potent maturation agents that result in a dendritic cell population that can induce an immune response against a tumor antigen in cancer patients. Moreover, the Examiner believes that one of ordinary skill in the art would have a reasonable expectation of success, since Bosch *et al.* teaches the effectiveness of these techniques in the generation of dendritic cells.

Applicants respectfully disagree with the rejection of claims 19-23 as being unpatentable over Matera *et al.* and Bernard *et al.*, as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, in further in view of Bosch *et al.*, 2001. Matera *et al.* and Bernard *et al.* are discussed above. Both references describe methods directed to the differentiation of activated monocytes and not non-activated monocytic dendritic cell precursors as set forth in the instant claims. In addition, both Matera and Bernard require GM-CSF in combination with some other agent, such as either the cytokine IL-4 or the hematopoietic protein prolactin for the differentiation of the isolated activated monocytes to form dendritic like cells.

Bosch *et al.* disclose a method for the production of immature dendritic cells that uses serum free conditions, but provides no additional details such as whether the method utilizes non-activated monocytic dendritic cell precursors or whether GM-CSF and IL-4 were used. Bosch *et al.* as set forth by the Examiner disclose the maturation of dendritic cells in the presence of BCG and IFN γ for the induction of an antigen specific cytotoxic T cell response. But, the references when considered alone or in any combination fail to teach a method for the production of immature dendritic cells from non-activated monocytic dendritic cell precursors in the presence of GM-CSF and without additional cytokines as presently claimed. As such, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 19-23 as being unpatentable over Matera *et al.* and Bernard *et al.* in further view of Bosch *et al.*

Claim 15 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Matera *et al.* and Bernard *et al.* as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, and further in view of Lewalle *et al.*, 2000 (of record). The alleged teachings of Matera *et al.* and Bernard *et al.* are described above. The Examiner has acknowledged they do not teach using a cryopreserved cell population to generate dendritic cells. Lewalle *et al.* is alleged by the Examiner to teach the generation of dendritic cells from frozen peripheral blood mononuclear cells. Furthermore, Lewalle *et al.* is alleged by the Examiner to teach that many clinical protocols are based on sequential injections of dendritic cells, and therefore it would be of practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. Based on these allegations and assertions that Examiner believes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the dendritic cell taught by Matera *et al.* and Bernard *et al.*, using frozen peripheral blood mononuclear cells, as taught by Lewalle *et al.*. Motivation for the ordinary artisan at the time the invention was made is alleged by the Examiner to be based on Lewalle *et al.* teaching that many clinical protocols are based on sequential injections of dendritic cells, and the practical importance to have frozen aliquots of the same peripheral blood mononuclear cells for these purposes. Furthermore, the Examiner believes that the ordinary artisan would have had

a reasonable expectation of success since Lewalle teaches that dendritic cells derived from frozen peripheral blood mononuclear cells retain their functional capacity.

Applicants respectfully disagree with the rejection of claim 15 as being unpatentable over Matera *et al.* and Bernard *et al.* as applied to claims 1, 3, 8, 9, 13, 14, 17 and 18 above, and further in view of Lewalle *et al.*, 2000. As above, Matera *et al.* and Bernard *et al.* when considered either alone or in any combination fail to teach the methods of the present invention. Lewalle *et al.* also does not disclose or suggest a method for differentiating non-activated human monocytic dendritic cell precursors into immature dendritic cells having decreased CD14 and having increased CD1a on the cell surface, comprising: providing a cell population comprising non-activated human monocytic dendritic cell precursors, and contacting the non-activated monocytic dendritic cell precursors in a culture vessel with a dendritic cell culture media supplemented with granulocyte-macrophage colony stimulating factor in the absence of additional cytokines under conditions that do not activate the monocytic dendritic cell precursors. As such, Lewalle *et al.* does not provide any feature of the invention that is not disclosed in Matera *et al.* and/or Bernard *et al.* Lewalle *et al.* is directed to the generation of dendritic cells from frozen peripheral blood mononuclear cells. Such a disclosure does not teach or suggest any method for the production of immature dendritic cells from non-activated monocytic dendritic cell precursors. The references when considered either alone or in any combination also do not provide or suggest that the skilled artisan would have any reasonable expectation of success in developing such a method. Therefore, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 15 as being unpatentable over Matera *et al.* and Bernard *et al.*, and further in view of Lewalle *et al.*

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an

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PATENT

early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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Schütt C et al. Human monocyte activation ind...[PMID: 2468604]

PMID - 2468604
OWN - NLM
STAT - MEDLINE
DA - 19890602
DCOM- 19890602
LR - 20061115
IS - 0165-2478 (Print)
VI - 19
IP - 4
DP - 1988 Dec
TI - Human monocyte activation induced by an anti-CD14 monoclonal antibody.
PG - 321-7
AB - An anti-CD14 mAb RoMo-1 rapidly induces in human monocytes a transient oxidative burst activity as detected by chemiluminescence assay. Pretreatment of these cells with the mAb markedly suppresses the monocyte chemiluminescence response to opsonized zymosan. In addition, the antibody induces a significant increase of IL-1 production and secretion by mononuclear cells, comparable to a similar effect of rIFN-gamma or LPS. Electron microscopy demonstrates internalization of the CD14 molecules after interaction with the mAb in a characteristic receptor-like manner.
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FAU - Schütt, C
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FAU - Ringel, B
AU - Ringel B
FAU - Nausch, M
AU - Nausch M
FAU - Bazil, V
AU - Bazil V
FAU - Horejsi, V
AU - Horejsi V
FAU - Neels, P
AU - Neels P
FAU - Walzel, H
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FAU - Jonas, L
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FAU - Siegl, E
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FAU - Friemel, H
AU - Friemel H
AU - et al.
LA - eng
PT - In Vitro
PT - Journal Article
PL - NETHERLANDS

TA - Immunol Lett
JT - Immunology letters
JID - 7910006
RN - 0 (Antibodies, Monoclonal)
RN - 0 (Antigens, CD14)
RN - 0 (Antigens, Differentiation, Myelomonocytic)
RN - 0 (Interleukin-1)
RN - 9010-72-4 (Zymosan)
SB - IM
MH - *Antibodies, Monoclonal
MH - Antigens, CD14
MH - *Antigens, Differentiation, Myelomonocytic
MH - Humans
MH - Interleukin-1/biosynthesis
MH - Luminescent Measurements
MH - Microscopy, Electron
MH - Monocytes/*immunology/metabolism/ultrastructure
MH - Zymosan/pharmacology
EDAT - 1988/12/01
MHDA- 1988/12/01 00:01
CRDT - 1988/12/01 00:00
PST - ppublish
SO - Immunol Lett. 1988 Dec;19(4):321-7.